Exhibit B

ANTICONVULSANT ENANTIOMERIC AMINO ACID DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to novel enantiomeric compounds and pharmaceutical compositions useful in the treatment of epilepsy and other CNS disorders.

BACKGROUND OF THE INVENTION

The predominant application of anticonvulsant drugs is the control and prevention of seizures associated with epilepsy or related central nervous system disorders. Epilepsy refers to many types of recurrent seizures produced by paroxysmal excessive neuronal discharges in the brain; the two main generalized seizures are petit mal, which is associated with myoclonic jerks, akinetic seizures, transient loss of consciousness, but without convulsion; and grand mal which manifests in a continuous series of seizures and convulsions with loss of consciousness.

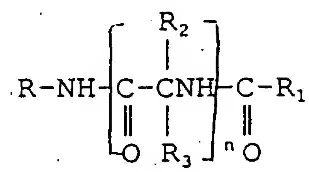
The mainstay of treatment for such disorders has been the long-term and consistent administration of anticonvulsant drugs. Most drugs in use are weak acids that, presumably, exert their action on neurons, glial cells or both of the central nervous system. The majority of these compounds are characterized by the presence of at least one amide unit and one or

more benzene rings that are present as a phenyl group or part of a cyclic system.

Much attention has been focused upon the development of anticonvulsant drugs and today many such drugs are well known. For example, the hydantions, such as phenytoin, are useful in the control of generalized seizures and all forms of partial seizures. The oxazolidinediones, such as trimethadione and paramethadione, are used in the treatment of nonconvulsive seizures. Phenacemide, a phenylacetylurea, is one of the most well known anticonvulsants employed today, while much attention has recently been dedicated to the investigation of the diazepines and piperazines. For example, U.S. Pat. Nos. 4,002,764 and 4,178,378 to Allgeier, et al. disclose esterified diazepine derivatives useful in the treatment of epilepsy and other nervous disorders. U.S. Pat. No. 3,887,543 to Nakanishi, et al. describes a thieno [2,3-e][1,4]diazepine compound also having anticonvulsant activity and other depressant activity. U.S. Pat. No. 4,209,516 to Heckendorn, et al. relates to triazole derivatives which exhibit anticonvulsant activity and are useful in the treatment of epilepsy and conditions of tension and agitation. U.S. Pat. No. 4,372,974 to Fish, et al. discloses a pharmaceutical formulation containing an aliphatic amino acid compound in which the carboxylic acid and primary amine are separated by three or four units. Administration of these compounds in an acid pH range

are useful in the treatment of convulsion disorders and also possess anxiolytic and sedative properties.

U.S. Pat. No. 5,378,729 to Kohn, et al. disclose compounds and pharmaceutical compositions having central nervous system (CNS) activity which are useful in the treatment of epilepsy and other CNS disorders having the following general formula:



R is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, and R is unsubstituted or is substituted with at least one electron withdrawing group, or electron donating group.

R_1 is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, each unsubstituted or substituted with an electron donating group or an electron withdrawing group and

R_2 and R_3 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, heterocyclic lower alkyl, lower

alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, or Z-Y wherein R_2 and R_3 may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;

Z is O, S, $S(O)_a$, NR_4, PR_4 or a chemical bond;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, halo, heterocyclic, or heterocyclic lower alkyl, and Y may be unsubstituted or substituted with an electron donating group or an electron withdrawing group, provided that when Y is halo, Z is a chemical bond, or

ZY taken together is $NR_4NR_5R_7$, NR_4OR_5, ONR_4R_7, OPR_4R_5, PR_4OR_5, SNR_4R_7, NR_4SR_7, SPR_4R_5, PR_4SR_7, $NR_4PR_5R_6$, $PR_4NR_5R_7$,

$$NR_4\underset{\underset{O}{\|}}{C}-R_5,\quad S\underset{\underset{O}{\|}}{C}R_5,\quad NR_4\underset{\underset{O}{\|}}{C}-OR_5,\quad S\underset{\underset{O}{\|}}{C}-OR_5$$

R_4, R_5 and R_6 are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein R_4, R_5 and R_6 may be unsubstituted or substituted with an electron withdrawing group or an electron donating group,

R_7 is R_6, $COOR_8$ or COR_8,

R_8 is hydrogen, lower alkyl, or aryl lower alkyl, and the aryl or alkyl group may be unsubstituted or substituted with an electron withdrawing group or an electron donating group and .

n is 1-4 and

a is 1-3.

Unfortunately, despite the many available pharmacotherapeutic agents, a significant percentage of the population with epilepsy or related disorders are poorly managed. Moreover, none of the drugs presently available are capable of achieving total seizure control, but unfortunately, most have disturbing side effects. Furthermore, many anticonvulsants have associated therewith liver toxicity.

Research is continuing in this area to find better and more effective anticonvulsant agents. Obviously, the ideal drug is one that has high pharmacological activity, minimal side effects and is relatively non-toxic and safe to the animal that is being treated. More specifically, the ideal anticonvulsant drug is one that satisfies the following four criteria: (1) has a high anticonvulsant activity, (expressed as ED_{50}); (2) has minimal neurological toxicity, (as expressed by the median toxic dose (TD_{50})), relative to its potency; (3) has a maximum protective index (sometimes known as selectivity or margin of safety), which measures the relationship between the doses of a drug required to produce undesired and desired effects, and is measured as the ratio between the median toxic dose and the median effective dose (TD_{50}/ED_{50}); and (4) is relatively safe as measured by the median lethal close (LD_{50})

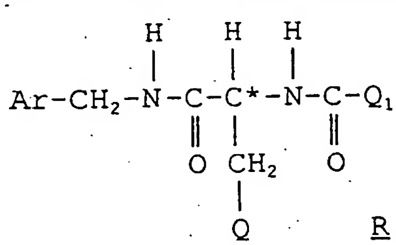
relative to its potency and is non-toxic to the animal that is being treated, e.g., it exhibits minimal adverse effects on the remainder of the treated animal, its organs, blood, its bodily functions, etc. even at high concentrations. Thus, for example, it exhibits little or no liver toxicity.

Heretofore, no anti-convulsant drug has been developed that has the following characteristics: maximum potency, minimal neurological toxicity, superior protective index and minimal liver toxicity.

However, the present inventor has found such a group of compounds that is generally potent, exhibit minimal neurologically toxicity, has a high protective index and is relatively non-toxic to the body organs, including the liver.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to N-benzyl-2-acetamido propionamide derivatives in the R configuration having the formula:



I

wherein

Ar is aryl which is unsubstituted or substituted with halo;

Q is lower alkoxy; and

Q_1 is CH_3.

The present invention contemplates employing the compound of Formula I in a pharmaceutical composition. Moreover, the administration of an effective amount of the present compounds in their pharmaceutically acceptable forms provides an excellent regime for the treatment of epilepsy, nervous anxiety, psychosis, insomnia, and other related central nervous disorders.

DETAILED DESCRIPTION OF THE INVENTION

The term "alkoxy" refers to an O-alkyl group attached to the main chain through an oxygen bridge, wherein alkyl is as defined hereinabove. The alkoxy groups are lower alkoxy groups containing one to six carbon atoms, and more preferably, one to three carbon atoms. The most preferred alkoxy groups are propoxy, isopropoxy, ethoxy and especially methoxy.

The term "aryl", when used alone or in combination, refers to a phenyl group which is unsubstituted or substituted with halo.

The term halo includes fluoro, chloro, bromo, iodo and the like. The preferred halo is fluoro.

It is preferred that Q in the compound of formula I is alkoxy having 1-3 carbon atoms. The most preferred alkoxy group is propoxy, isopropoxy, ethoxy and especially methoxy.

The Ar group as defined herein, is phenyl, which may be unsubstituted or substituted as defined herein. It is most preferred that the aryl group, i.e., phenyl, is unsubstituted or substituted with only one halo group. It is more preferred that if substituted, the halo substituent is in the para or meta position. It is even more preferred that the phenyl group is unsubstituted.

Examples of the compounds of the present invention include:

(R)-N-Benzyl-2-acetamido-3-methoxy propionamide,

(R)-N-(3-Fluorobenzyl)-2-acetamido-3-methoxypropionamide,

(R)-N-(4-Fluorobenzyl)-2-acetamide-3-methoxypropionamide,

(R)-N-Benzyl-2-acetamido-3-ethoxy propionamide.

As indicated by the asterisk in formula I, the compounds of the present invention contain at least one asymmetric carbon and the stereochemistry at the asymmetric carbon is in the R configuration. The inventor has found that the R stereoisomer is significantly more efficacious than the corresponding S enantiomer or a racemic mixture thereof.

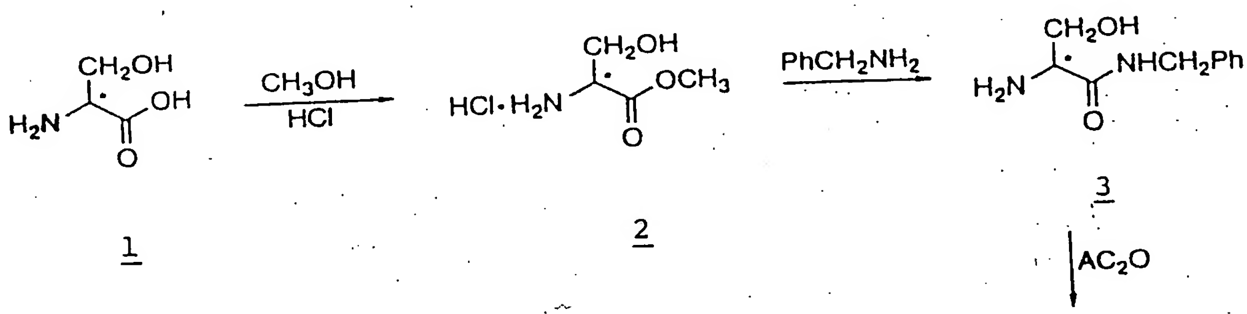
It is preferred that the compound of the present invention be substantially pure, i.e., substantially free from impurities. It is most preferred that the compounds of the present invention be at least 75% pure (w/w) and more preferably greater than about 90% pure (w/w) and most preferably greater than about 95% pure (w/w).

It is also preferred that the compounds of the present invention be substantially enantiomerically pure, i.e., substantially free from the corresponding S isomer. It is more preferred that the compounds of the present invention contain at least 90% (w/w) R stereoisomer, and most preferably greater than about 95% (w/w) in the R stereoisomer. Thus, the present invention contemplates compounds having at most about 10% S isomer (w/w), and even more preferably less than about 5% S isomer (w/w).

The compounds of the present invention in the R form are prepared by art recognized techniques from commercially available starting materials.

An exemplary procedure is outlined in Scheme 1 hereinbelow:

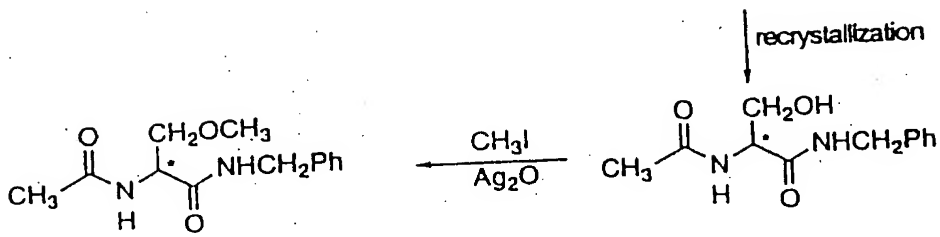
Scheme 1



1

2

3



5 4

A D serine molecule (1) is esterified under acylation conditions with an alcohol, such as acidic methanol, to provide the corresponding ester (2). 2 is reacted with $ArCH_2NH_2$, such as benzylamine, under acylation conditions to form the corresponding amide (3). Acylation of the free amino group, with an acylating derivative of $Q_1\underset{\underset{\displaystyle O}{\|}}{C}\text{-OH}$,

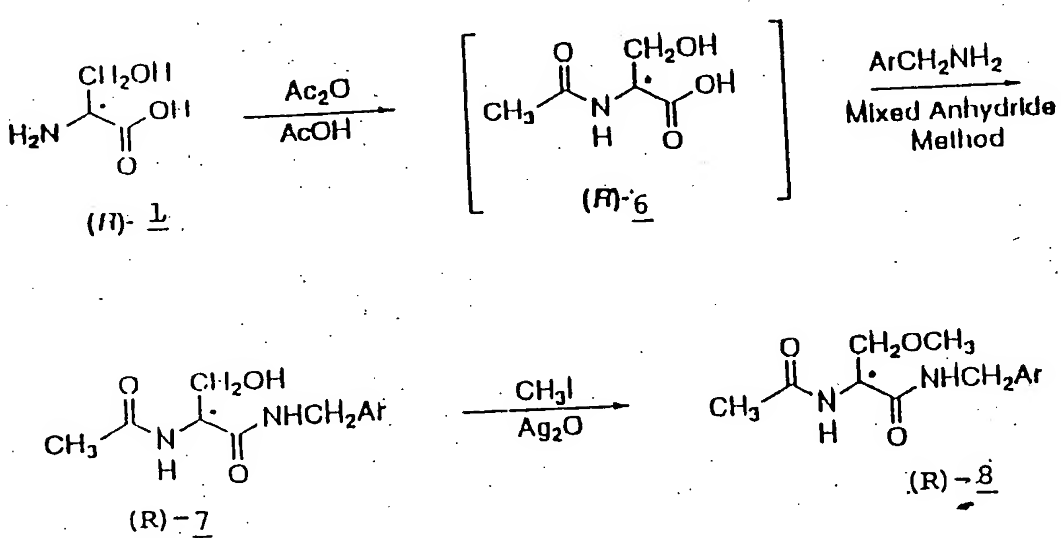
such as acetic acid, or lower alkyl ester of acetic acid, or acetic anhydride provides the hydroxymethyl derivative, i.e.,

$$\text{Ar CH}_2\ \overset{\displaystyle H}{N}-\underset{\underset{\displaystyle O}{\|}}{C}-\overset{\displaystyle H}{\underset{\underset{\displaystyle CH_2\text{-OH}}{|}}{C}}-\overset{\displaystyle H}{N}-\overset{\overset{\displaystyle O}{\|}}{C}-Q_1 \qquad (4)$$

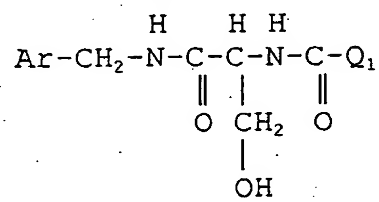
The enantiopurity of 4 was determined by techniques known in the art, including melting point, optical rotation and ^1H NMR upon addition of an organic acid in the R-configuration, such as R(-)- mandelic acid. Crystallization of 4 was repeated until the desired enantiopurity thereof was achieved. The product of 4 is converted to the ether under Williamson conditions by reacting it with QX, wherein Q is as defined herein above and X is good leaving groups, such as OTs, OMs, or halide (e.g., CH_3I) and the like in the presence of base (e.g., Ag_2O) to form the product (5) having Formula I.

Another variation is depicted in Scheme 2.

Scheme 2



For example, beginning with D-serine (1), treatment with an acylating derivative of acetic acid. such as acetic anhydride in acetic acid, gives the corresponding amide 6 which is then reacted with $ArCH_2NH_2$ under mixed anhydride coupling reaction conditions, as described by Anderson, et al., in JACS, 1967, 89, 5012-5017, the contents of which are incorporated herein by reference, to give the corresponding compound of the formula:



R

e.g., 7. Alkylation of this R-product in the presence of base under Williamson conditions, such as methyl iodide in Ag_2O, provides a product of Formula I(8).

The active ingredients of the therapeutic compositions and the compounds of the present invention exhibit excellent anticonvulsant activity when administered in amounts ranging from about 1 mg to about 100 mg per kilogram of body weight per day. This dosage regimen may be adjusted by the physician to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic

situation. A decided practical advantage is that the active compound may be administered in an convenient manner such as by the oral, intravenous (where water soluble), intramuscular or subcutaneous routes.

The active compound may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly into the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 80% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 5 and 1000 mg of active compound.

The tablets, troches, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a

disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations. For example, sustained release dosage forms are contemplated wherein the active ingredient is bound to an ion exchange resin which, optionally, can be coated with a diffusion barrier coating to modify the release properties of the resin.

The active compound may also be administered parenterally or intraperitoneally. Dispersions can also be prepared in glycerol, liquid polyethylene

glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of

the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated.

Supplementary active ingredients can also be incorporated into the compositions.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifics for the novel dosage unit forms of the invention are dictated by and directly, dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore described. A unit dosage form can, for example, contain the principal active compound in amounts ranging from about 5 to about 1000 mg. Expressed in proportions, the active compound is generally present in from about 1 to about 750 mg/ml of carrier. In the

case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

Unless indicated to the contrary, percentages are by weight.

As used herein, the term lower alkyl refers to an alkyl group containing 1-6 carbon atoms which may be straight chained or branched.

For a better understanding of the present invention reference is made to the following description and examples.

GENERAL METHODS

Melting points were determined with a Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on Perkin-Elmer 1330, 283 and a Mattson Genesis spectrometer and were calibrated against the 1601 cm^{-1} bond of polystyrene. Absorption values are expressed in wave-numbers (cm^{-1}). Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were taken on Nicolet NT-300 and General Electric QE-300 NMR instruments. Chemical shifts (δ) are in parts per million (ppm) relative to Me_4Si and coupling constants (J values) are in hertz. All chemical ionization mass spectral investigations were conducted on Finnegan MAT TSQ-70 instrument. Ethyl α-acetamido cyanoacetate was obtained from Aldrich Chemical Co. Microanalyses were provided by Atlantic Microlab Inc. (Norcross, Ga). Thin layer chromatography was performed on precoated silica gel GHLF microscope slides (2.5 x 10 cm; Analtech No. 21521).

EXAMPLE 1

(R)-N-Benzyl-2-Acetamido-3-methoxypropionamide

Hydrochloric acid (8.00g, 219.4 mmol) was passed into MeOH (250 mL) and then D-Serine (20.00g, 190.3 mmol) was added. The reaction solution was heated at reflux (18 hours), benzylamine (81.6 mL, 761 mmol) was added and then the reaction was heated for an additional eighteen hours. The solvent was removed under reduced pressure, the insoluble salts filtered, and the excess benzylamine was removed under high vacuum (Kugelrohr). The residue was dissolved in water (100 mL), and the product was extracted with $CHCl_3$ (8 x 200 mL). The organic layers were combined, dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was triturated with Et_2O (150 mL) and filtered to give 10.0 g (27%) of the product R-enriched N-benzyl 2-aminohydracrylamide, as a white solid: mp 74-78°C.; $[\alpha]_D^{23}$ (c=1, MeOH) = -1.6°, Rf 0.30 (10% MeOH-$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ1.87 (br s, NH_2), 3.23 (t, J=5.4 Hz, CH), 3.39-3.55 (m, CH_2OH), 4.28 (d, J=5.7 Hz, $NHCH_2$) 4.76 (t, J=5.4 Hz, CH_2OH), 7.18-7.32 (m, 5PhH), 8.34 (t J=5.7 Hz, NH), ^{13}C NMR (DMSO-d_6) 41.8 ($NHCH_2$), 56.9 (CH), 64.3 (CH_2OH), 126.6 (C_4'), 127.0 (2C_2' or 2C_3'), 128.1 (2C_2' or 2C_3'), 139.5 C_1'), 173.3 (C(O)NH) ppm, MS (+Cl) (rel intensity),

195 (M^+ +1, 53), 117 (100), Mr(+Cl) 195.113 56 (M^+ +1) (calcd. for $C_{10}H_{15}N_2O_2$, 195.11335).

To a stirred methylene chloride suspension (100 ml) of R enriched N-benzyl 2-aminohydracrylamide (10.00 g, 51.5 mmol) was added acetic anhydride (5.8 mL, 61.8 mmol), and the reaction suspension was stirred at room temperature (1 hour). The solvent was removed under reduced pressure to give a white solid. The product was triturated with Et_2O (250 mL) to give 7.60g (62%) of enriched R-N-benzyl-2-acetamidohydracrylamide as a white solid. The reaction product was recrystallized (2x) using EtOH to give 3.50 g (29%) of the R-N-benzyl-2-acetamidohydracrylamide mp 148-149°C; $[\alpha]_D^{23}$ (c=1, MeOH)=+22.4°; Rf 0.40 (10% MeOH -$CHCl_3$); IR (KBr) 3295, 3090, 2964, 1642, 1533, 1376, 1281, 1051, 705 cm; ^1H NMR (DMSO -d_6) δ1.86 (s,C(O)CH_3), 3.57 (dd, J=5.7, 5.7 Hz, CH_2 OH), 4.25-4.31(m,CH), 4.27 (d, J=5.7 Hz, $NHCH_2$), 4.92 (t, J=5.7 Hz, CH_2OH), 7.18-7.32 (m, 5 PhH) 7.94 (d, J=7.8Hz, NH), 8.38 (t, J=5.7 H, NH); addition of excess R-(-) mandelic acid to a $CDCl_3$ solution of R-N-benzyl 2-acetamidohydracrylamide prepared hereinabove gave only one signal for the acetyl methyl protons; ^{13}C NMR (DMSO-d_6) 22.7 (C(O)CH_3), 42.0 (CH_2NH), 55.6 (CH), 61.8(CH_2OH), 126.7 (C_4'), 127.0 ($2C_2$' or $2C_3$'), 128.2 ($2C_2$' or $2C_3$'), 139.4 (C_1'), 169.5 (C(O)CH_3 or C(0)NH), 170.3 (C(O)CH_3 or C(O)NH) ppm; MS (+ Cl) rel intensity) 237(M^++1, 100), 219(8); Mr(+Cl)

237.12388 [M^{+}+1] (calcd for C_{12} H_{17} N_2 O_3 237.12392); Anal ($C_{12}H_{16}N_2O_3$), C,H,N.

To a stirred acetonitrile solution (300mL) of (R)-N-benzyl (α-Acetamidohydroacrylamide (2.36g, 10mmol) was successively added Ag_2O (11.59g, 50 mmol) and methyl iodide (6.2 mL, 100 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 days. The insoluble salts were filtered, and the solvents were removed in vacuo to give a white solid. The residue was filtered with Et_2O (100 mL) to give 2.20g (88%) of the above-identified product.

mp 143-144°C; $[\alpha]_D^{23}$ (c=1, MeOH)=+16.4°; Rf0.47 (10% MeOH-$CHCl_3$); IR (KBr) 3289,3086, 2923, 2876, 2819, 1636, 1547, 1138, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ2.04 (s, C(O)CH_3), 3.38 (s, OCH_3), 3.43 (dd, J=7.8, 9.0 Hz, CHH'OCH_3), 3.82 (dd, J=4.2, 9.0 Hz, CHH'OCH_3), 4.48(d, J=6.0 Hz, $NHCH_2$), 4.51-4.57 (m,CH), 6.44 (br d, J=5.4 Hz, NH), 6.75 (br s, NH), 7.25-7.37 (m, 5 PhH), addition of excess (R)-(-)-mandelic acid to a $CDCl_3$ solution of (R)-18 gave only one signal for the acetyl methyl and ether methyl protons; ^{13}C NMR ($CDCl_3$) 23.2 (C(O)CH_3), 43.5 (CH_2NH), 52.4 (CH), 59.1 (OCH_3), 71.7 (CH_2OCH_3), 127.4 (C_4'), 127.5 (2C_2' or 2C_3'), 128.7 (2C_2' or 2C_3'), 137.9 (C_1'), 169.9 (C(O)CH_3 or C(O)NH), 170.3 (C(O)CH_3 or C(O)NH) ppm; MS (+Cl) (rel intensity) 251 (M^{+}+1, 100), 219(6); Mr (+Cl)251.139 76 [M^{+}+1] (calcd for $C_{13}H_{19}N_2O_3$ 251.139 57); Anal. ($C_{13}H_{18}N_2O_3$)C,H,N.

EXAMPLE 2

Another Synthesis of (R)-N-Benzyl 2-Acetamido-3-methoxy propionamide.

(a) Improved Synthesis of (R)-N-Benzyl 2-Acetamidohydracrylamide

To a stirred AcOH (20mL) suspension of D-serine (5.26 g, 50 mmol) was added Ac_2O (4.7 mL, 50 mmol), and then the reaction suspension was stirred at room temperature (24 hours). The AcOH was removed in vacuo to give an oily residue, and then THF (150 mL) was added to the residue. The THF suspension was cooled to -78°C under N_2 and 4-methylmorpholine (11.0 mL, 100 mmol) was added. After stirring for two minutes, isobutyl chloroformate (13.0 mL, 100 mmol) was added leading to the precipitation of a white solid. The reaction was allowed to proceed for two additional minutes and then benzylamine (10.4 mL, 100 mmol) was added at -78°C. The reaction mixture was allowed to stir at room temperature (30 minutes) and the 4-methylmorpholine hydrochloride salt was filtered. The organic layer was concentrated in vacuo. The product was purified by flash column chromatography on SiO_2 gel (10% MeOH-$CHCl_3$) to give 3.89 g (33%) as a white solid mp 147-148°C, $[\alpha]_D^{23}$ (C=1, MeOH) = +21.7°; ^{1}H NMR (DMSO-d_6) δ 1.86 (s, C(O) CH_3), 3.57 (dd, J = 5.1, 5.1 Hz, CH_2O) 4.27-4.31 (m, CH_2NH, CH), 4.90 (t, J=5.1 Hz, OH), 7.20-7.31 (m, 5

PhH), 7.93, (d, J = 8.1 Hz, NH), 8.37 (t, J = 6.0 Hz, NH), addition of excess (R)-(-)-mandelic acid to a $CDCl_3$ solution of the product of (a) gave only one signal for the acetyl methyl protons.

(b) (R)-N-Benzyl-2-Acetamido-3-methoxypropionamide.

To the compound prepared in (a) (1.42 g, 6 mmol) in a stirred solution (300 ml) of CH_3CN was successively added Ag_2O (6.95 g, 30 mmol) and methyl iodide (3.7 mL, 60 mmol) and stirred at room temperature for 4 days. The insoluble salts were filtered and the solvent was removed in vacuo to give a white solid. The white solid was triturated with Et_2O (100 mL) to given 1.30 g (87%) of the above-identified compound: mp 143-144°C, $[\alpha]_D^{23}$ (c = 1, MeOH) = + 16.0°; ^1H NMR ($CDCl_3$) δ 2.04 (s, $C(O)CH_3$), 3.38(s, OCH_3), 3.44 (dd, J=7.5, 9.0 Hz, CH H^1 OCH_3), 3.81 (dd, J = 4.2, 9.0 Hz, CHH'OCH_3), 4.48 (d, J = 5.7 Hz, $NHCH_2$), 4.52-4.58 (m, CH), 6.46 (br d, J = 5.7 Hz, NH), 6.78 (br, s, NH), 7.25-7.37 (m, 5 Ph H), addition of excess (R)-(-)-mandelic acid to a $CDCl_3$ solution of the above-identified compound gave only one signal for the acetyl and ether methyl protons.

EXAMPLE 3

R-N-(3-Fluorobenzyl)2-Acetamido-3-Methoxypropionamide.

(a) R-N-(3-Fluorobenzyl)-2-Acetamido-hydracrylamide.

Utilizing the procedure of Example 2(a) with the following amounts of D-serine (5.26 g, 50 mmol), Ac_2O (5.7 mL, 60 mmol), 4-methylmorpholine (11.0 mL, 100 mmol), isobutyl chloroformate (13.0 mL, 100 mmol) and substituting 3-fluorobenzylamine (11.8 mL, 100 mmol) for benzylamine, gave 4.20 g (33%) of the above compound as a white solid after purification: mp 137-138°C; $[\alpha]_D^{23}$ (c = 1, MeOH) = +20.8°; R_f 0.32 (10% MeOH-$CHCl_3$); IR (KBr) 3282, 3101, 2944, 1636, 1542, 1252, 1050, 779, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ1.87 (s, C(O)CH_3), 3.56-3.63 (m, CH_2OH), 4.29 (d, J = 6.0 Hz, CH_2NH), 4.25-4.30 (m, CH), 4.95 (t, J = 5.4 Hz, CH_2OH), 7.00-7.09 (m, 3 ArH), 7.29-7.30 (m, 1 ArH), 7.97 (d, J = 8.1 Hz, NH), 8.44 (t, J = 6.0 Hz, NH), addition of excess (R)-(-)-mandelic acid to a $CDCl_3$ solution of this product gave only one signal for the acetyl methyl portions; ^{13}C NMR (DMSO-d_6) 22.7 (C(O)CH_3), 41.6 (CH_2N), 53.4 (CH), 61.7 (CH_2 OH), 113.3 (d, J_{CF} =20.0 Hz, (C_2' or C_4'), 113.6 (d, J_{CF}=20.7 Hz, C_2' or C_4'), 122.9 (C_6'), 130.1 (d, J_{CF}= 8.2 Hz, $C_{5'}$), 142.6 (d, J_{CF} = 7.0 Hz, $C_{1'}$), 162.3 (d, J_{CF} = 241.4 Hz, $C_{3'}$), 169.6 (C(O)CH_3 or C(O)NH), 170.5 (C(O)CH_3 or C(O)NH) ppm; MS

(+Cl) (rel. intensity) 255 (M^+ + 1, 100); M_r(+Cl) 255.113 54 [M^+ + 1] (calcd. for $C_{12}H_{16}FN_2O_3$ 255.114 50); Anal. ($C_{12}H_{15}FN_2O_3$) C, H, N.

(b) (R)-(N-3-Fluorobenzyl)-2-Acetamido-3-methoxypropionamide.

To the product of (a) (2.54 g, 10 mmol) in a stirred CH_3CN solution was successively added Ag_2O (11.59 g, 50 mmol) and MeI (6.2 mL, 100 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 days. The insoluble salts were filtered and the solvent was removed <u>in vacuo</u> to give a white solid which was triturated with Et_2O (100 mL) to give a crude product of the above identified compound. The product was further purified by flash chromatography on SiO_2 gel (10% MeOH-$CHCl_3$) to give 2.00 g (75%) of the above-identified compound: mp 150-151°C; $[\alpha]_D^{23}$ (c = 1, MeOH) = +16.5°C; R_f 0.50 (10% MeOH-$CHCl_3$); IR (KBr) 3287, 3072, 2928, 2883, 1634, 1548, 1256, 1142, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.05 (s, C(O)CH_3), 3.40 (s, OCH_3), 3.44-3.47 (m, CHH'OCH_3), 3.81-3.85 (m, CHH'OCH_3), 4.41-4.50 (m, $NHCH_2$), 4.53-4.59 (m, CH), 6.42 (br s, NH), 6.81 (br s, NH), 6.93-7.05 (m, 3 PhH), 7.26-7.31 (m, 1 PhH); addition of excess (R)-(-)-mandelic acid to a $CDCl_3$ solution of the above identified compound gave only one signal for the acetyl methyl protons and ether methyl protons; ^{13}C NMR (DMSO-d_6) 22.8 (C(O)CH_3), 42.7 (CH_2N), 52.6 (CH), 58.9 (OCH_3), 72.0 (CH_2OCH_3), 114.0 (d, J_{CF} = 21.5 Hz, $C_{2'}$ and $C_{4'}$), 122.7 ($C_{6'}$), 129.9 (d, J_{CF} = 7.7 Hz, $C_{5'}$),

140.6 (d, J_{CF} = 6.8 Hz, $C_{1'}$), 162.9 (d, J_{CF} = 244.4 Hz, $C_{3'}$), 170.2 ($C(O)CH_3$ or C(O)NH), 170.5 ($C(O)CH_3$ or C(O)NH) ppm; MS (+Cl) (rel. intensity) 269 (M^+ + 1, 100); M_r (+Cl) 269.129 31 [M^+ + 1] (calcd for $C_{13}H_{18}FN_2O_3$ 269.130 15); Anal. ($C_{13}H_{17}FN_2O_3$) C, H, N.

EXAMPLE 4

(R)-N-(4-Fluorobenzyl)2-Acetamido-3-Methoxypropanamide.

(a) (R)-N-(4-Fluorobenzyl)2-Acetamido-hydracrylamide.

Utilizing the procedure of Example 2(a) with the following amounts of D-serine (5.26 g, 50 mmol), Ac_2O (5.7 mL, 60 mmol), 4-methylmorpholine (11.0 mL, 100 mmol), and isobutyl chloroformate (13.0 mL, 100 mmol) and substituting 4-fluorobenzylamine (11.8 mL, 100 mmol) for benzylamine, the above-identified compound was prepared as a white solid after purification (4.08 g, 32%); mp: 169-170°C; $[\alpha]_D^{23}$ (c = 1, MeOH) = +17.6°; R_f 0.31 (10% MeOH-$CHCl_3$); IR (KBr) 3289, 3101, 3071, 2936, 1632, 1565, 1543 1508, 1214, 1053, 814 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.86 (s, $C(O)CH_3$), 3.56 (6, J = 5.4 Hz, CH_2OH), 4.25 (d, J = 6.0 Hz, CH_2NH), 4.25-4.29 (m, CH), 4.91 (t, J = 5.4 Hz, CH_2OH), 7.08-7.14 (m, $2C_{2'}H$), 7.25-7.29 (m, $2C_{3'}H$), 7.93 (d, J = 7.8 Hz, NH), 8.39 (d, J = 6.0 Hz, NH), addition of excess (R)-(-)-mandelic acid to a $CDCl_3$ solution of the above-identified compound gave only one signal for the acetyl methyl protons; ^{13}C NMR (DMSO-d_6) 22.7 ($C(O)CH_3$), 41.3 (CH_2N), 55.3 (CH), 61.7 (CH_2OH), 114.8 (d, J_{CF} = 21.8 Hz, $2C_{3'}$), 128.9 (d, J_{CF} = 8.0 Hz, $2C_{2'}$), 135.6 ($C_{1'}$), 161.1 (d, J_{CF} = 240.1 Hz, $C_{4'}$), 169.4 ($C(O)CH_3$ or C(O)NH), 170.3 ($C(O)CH_3$ or C(O)NH) ppm; MS (+Cl) (rel. intensity) 255 (M^+ + 1,

100); M_r(+Cl) 255.113 60 [M^+ + 1] (calcd for $C_{12}H_{16}FN_2O_3$ 255.114 50); Anal. ($C_{12}H_{15}FN_2O_3 \cdot 0.2H_2O$) C, H, N.

(b) R-N-(4-Fluorobenzyl)2-Acetamido-3-methoxypropanamide.

Following the procedure of Example 3(b) to the product of Example 4(a) (2.54 g, 10 mmol) in a stirred CH_3CN solution (300 mL) was successively added) Ag_2O (11.59 g, 50 mmol) and MeI (6.2 mL, 100 mmol) at room temperature and then stirred for 7 days. The insoluble salts were filtered, and the solvent was removed in vacuo to given a white solid. The white solid was triturated with Et_2O (100 mL) to give a crude product. The crude product was further purified by flash column chromatography (10% MeOH-$CHCl_3$) to give 2.00 g (75%) of the above product; mp: 144-145°C; $[\alpha]_D^{23}$ (c = 1, MeOH) = +12.0°; R_f0.52 (10% MeOH-$CHCl_3$); IR (KBr) 3281, 3102, 3072, 2959, 1632, 1547, 1513, 1223, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C(O)CH_3), 3.38 (s, OCH_3), 3.39-3.46 (m, CHH'OCH_3), 3.80-3.84 (m, CHH'OCH_3), 4.44 (br d, J = 5.4 Hz, CH_2NH), 4.48-4.56 (m, CH), 6.42 (br s, NH) 6.76 (br s, NH), 6.99-7.05 (m, 2 PhH), 7.21-7.31 (m, 2 PhH), addition of excess (R)-(-)-mandelic acid to a $CDCl_3$ solution of the above-identified product gave only one signal for the acetyl methyl portions and ether methyl portions, ^{13}C NMR ($CDCl_3$) 22.9 (C(O)CH_3), 42.6 (CH_2N), 52.5 (CH), 58.9 (OCH_3), 72.0 (CH_2OCH_3), 115.3 (d, J_{CF} = 22.0 Hz, $2C_{3'}$), 129.0 (d, J_{CF} = 6.9 Hz, $2C_{2'}$), 133.7 ($C_{1'}$), 161.9 (d, J_{CF} = 245.3 Hz, $C_{4'}$), 170.1 (C(O)CH_3 or

C(O)NH), 170.4 (C(O)CH_3 or C(O)NH) ppm; MS (+Cl) (rel. intensity) 269 (M^+ + 1, 100); M_r (+Cl) 269.129 66 [M^+ + 1] (calcd for $C_{13}H_{18}FN_2O_3$ 269.130 15); Anal. ($C_{13}H_{17}FN_2O_3$) C, H, N.

COMPARATIVE EXAMPLE 1

Preparation of N-Acetyl-D,L-alanine-N'-benzylamide

Acetic anhydride (2.20 g, 0.022 mol) was slowly added to a methylene chloride solution (30 mL) of D,L-alanine-N-benzylamide (3.80 g, 0.021 mol) and allowed to stir at room temperature (3h). The mixture was then successively washed with H_2O (15 mL), dried (Na_2SO_4) and concentrated _in vacuo_. The residue was recrystallized from CH_2Cl_2.

Yield: 2.50 g (54%). mp 139°-141°C.

^1H NMR (DMSO-d_6): δ1.22 (d, J = 7.1 Hz, 3H), 1.84 (s,3H), 4.04-4.50 (m,3H), 7.26 (s,5H), 8.11 (br d, J = 7.3 Hz, 1H), 8.42 (br t, J = 6 Hz, 1H).

^{13}C NMR (DMSO-d_6): 18.2, 22.4, 41.9, 48.2, 126.5, 126.9, 128.1 139.4, 168.9, 172.4 ppm.

IR ($CHCl_3$) 3440, 3300, 3005, 1660, 1515 cm^{-1}.

Mass spectrum (CI mode), m/e: 221 (P + I); mol wt. 220.1208 (calculated for $C_{12}H_{16}N_2O_2$, 220.1212).

COMPARATIVE EXAMPLES 2 AND 3

Preparation of N-Acetyl D and L-amino acid N-benzylamides

General procudure: The D or L amino acid amide (11 mmol) was dissolved in dichloromethane (15 mL) and then acetic anhydride (1.23g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (18h) and then concentrated to dryness. The residue was crystallized from chloroform/hexane.

COMPARATIVE EXAMPLE 2

N-Acetyl-D-alanine-N'-benzylamide

Yield: 1.36 g (56%). mp 139°-141°C. $[\alpha]_D^{23}$ = +36.2 (c 2.5, MeOH).

^{1}H NMR (80 MHz, DMSO-d_6): δ1.25 (d, J = 7.1 Hz, 3H), 1.86 (s, 3H), 10-4.50 (m,1H), 4.30 (d, J= 6.0 Hz, 2H), 7.26 (s, 5H), 8.09 (d, J = 7.3 Hz, 1H), 8.40 (t, J = 6.0 Hz, 1H).

^{13}C NMR (80 MHz, DMSO-d_6): 18.3, 22.5, 42.0, 48.4, 126.6, 127.0 (2C), 128.2 (2C), 139.4, 169.2, 172.5 ppm.

IR (KBr): 3290, 1635 (br), 1540, 1455, 700, 695 cm^{-1}.

Mass spectrum, m/e (relative intensity): 221 (30), 114 (20), 106 (40), 91 (80), 87 (100), 77 (5), 72 (20), 65 (5).

Elemental analysis calculated for $C_{12}H_{16}N_2O_2$ 65.42% C; 7.34% H; 12.72% N. Found 65.31% C; 7.28% H; 12.63% N.

COMPARATIVE EXAMPLE 3

N-Acetyl-L-alanine-N'-benzylamide

Yield: 1.11 g (46%). mp 139°-142°C. $[\alpha]_D^{23}$ = -35.3 (c 2.5, MeOH).

^{1}H NMR (80 MHz, DMSO-d_6): δ 1.23 (d, J = 7.2 Hz, 3H), 1.86 (s, 3H), 4.26-4.35 (m, 1H), 4.29 (d, J = 5.8 Hz, 2H), 7.22-7.33 (s,5H), 8.10 (d, J = 7.4 Hz, 1H), 8.42 (t, J = 5.8 Hz, 1H).

^{13}C NMR (80 MHz, DMSO-d_6): 18.3, 22.6, 42.0, 48.4, 126.7, 127.0 (2C), 128.3 (2C) 139.5, 169.2, 172.6 ppm.

IR (KBr): 3290, 1635 (br), 1545, 1450, 700, 695 cm^{-1}.

Mass spectrum, m/e (relative intensity): 221 (40), 114 (40), 106 (80), 106 (80), 91 (75), 87 (100), 77 (5), 72 (15), 65 (5).

Elemental analysis calculated for $C_{12}H_{16}N_2O_2$ 65.42% C; 7.34% H; 12.72% N. Found 65.58% C; 7.32% H; 12.43% N.

COMPARATIVE EXAMPLE 4

Preparation of D,

L-2-Acetamido-N-benzyl-2-methoxyacetamido

To a methanolic solution (180 mL) of methyl 2-acetamido-2-methoxyacetate (8.73 g, 54 mmol) was rapidly added benzylamine (8.68 g, 8.80 mL, 81 mmol) and then the mixture was stirred at 50°C (3 days) during which time a beige precipitate appeared. The solvent was removed *in vacuo* and the resulting precipitate was recrystallized from tetrahydrofuran (2X) to given 7.67 g (32%) of the desired product as beige crystals: R_f 0.35 (95:5 chloroform/methanol).

mp 145°-146°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ2.06 (s, CH_3CO), 3.37 (2,CH_3O), 4.40-4.35 (m, CH_2), 5.52 (d, J = 8.7 Hz, CH), 7.12 (d, J = 8.7 Hz, NH), 7.20-7.40 (m, Ph, NH).

^{13}C NMR (300 MHz, $CDCl_3$): 23.03 (CH_3CO), 43.51 (CH_2), 55.84 (CH_3O), 78.94 (CH), 127.62 (C_4"), 127.70 ($2C_2$" or $2C_3$"), 128.70 ($2C_2$ or $2C_3$"), 137.45 (C_1"), 166.91 ($COCH_3$), 171.57 (CONH) ppm.

IR (KBr): 1260, 1825 (br), 1550, 1505, 1435, 1390, 1370, 1230, 1120, 1050 935, 890, 690 cm^{-1}.

Mass spectrum, m/e (relative intensity): 237 (1), 205 (2), 177 (2), 163 (4), 146 (1), 134 (1), 121 (2), 106 (26), 102 (98), 91 (95), 77 (13), 61

(100). Elemental analysis calculated for $C_{12}H_{16}N_2O_3$ 61.00% C; 6.83% H; 11.86% N. Found 60.91% C; 6.85% H; 11.66% N.

COMPARATIVE EXAMPLES 5-7

Synthesis of Unsubstituted and Substituted-α-Acetamido-N-benzyl-2-furanacetamides

General Procedure. 4-Methylmorpholine (1 equiv) was added to a solution of α-acetamido-2-furanacetic acid (1 equiv) in dry tetrahydrofuran (75 mL/10 mmol) at -10 to -15°C under N_2. After stirring (2 min.), isobutyl chloroformate (1 equiv) was added leading to the precipitation of a white solid. The reaction was allowed to proceed for 2 additional minutes and then a solution of the substituted benzylamine (1 equiv) in tetrahydrofuran (10 mL/10mmol) was added over 5 min. at -10 to -15°C. The reaction mixture was allowed to stir at room temperature for 5 min. and then the 4-methylmorpholine hydrochloride salt filtered. The organic layer was concentrated <u>in vacuo</u>, and the residue was triturated with ethyl acetate, and the remaining white solid filtered. Concentration of the ethyl acetate layer led to additional amounts of the white solid. The desired product was purified by either recrystallization or flash chromatography of the combined solid material.

COMPARATIVE EXAMPLE 5

(D,L)-α-Acetamido-N-benzyl-2-furanacetamide

Benzyl amine (0.27 g, 2.56 mmol) and racemic α-acetamido-2-furanacetic acid (0.47 g, 2.56 mmol) gave the desired compound. The product was recrystallized from ethyl acetate to give a white solid.

Yield: 0.46 g (65%) R_f 0.30 (98:2 chloroform/methanol). mp 177°-178°C.

^1H NMR (DMSO-d_6) δ1.90 (s,CH_3), 4.31 (d, J = 6.0 Hz, CH_2), 5.58 (d, J = 8.1 Hz, CH), 6.27-6.33 (m, C_3H), 6.40-6.44 (m, C_4H), 7.20-7.36 (m, 5 PhH), 7.60-7.64 (m, C_5H), 8.57 (d, J = 8.1 Hz, NH), 8.73 (t, J = 6.0 Hz, NH).

COMPARATIVE EXAMPLE 6

(D)-(-)α-Acetamido-N-benzyl-2-furanacetamide

Starting with D-α-acetamido-2-furanacetic acid (2.45 g, 13.38 mmol) and benzylamine (1.43 g, 13.38 mmol), the desired product was obtained. Yield: 2.54 g (70%). The product was further recrystallized from ethyl acetate to give the title compound.

Yield: 2.30 g mp 196°-197°C. $[\alpha]^{26}D[c = 1, MeOH] = 78.3°$. Addition of R(-)-mandelic acid to a $CDCl_3$ solution the product gave only one signal for the acetamide methyl protons. Mass spectrum, m/e (relative intensity) 272 (M+, 2), 184 (2), 165 (2), 140 (8), 139 (88), 138 (34), 97 (46), 96 (100), 91 (63).

Elemental analysis: calculated: 66.16%C; 5.92% H; 10.29% N. Found: 66.09% C; 6.01% H; 10.38% N.

COMPARATIVE EXAMPLE 7

(L)-(+)-α-Acetamido-N-benzyl-2-furanacetamide

L-α-acetamido-2-furanacetic acid (2.83 g, 15.46 mmol) and benzylamine (1.65 g. 15.4G mmol) gave 3.80 g of the enriched desired product. ^{1}H NMR analysis with R(-)-mandelic acid showed that it was greater than 80% enriched in the title compound. The pure L-enantiomer was obtained by recrystallization from absolute ethanol.

Yield: 1.60 g. mp 196°-197°C. $[\alpha]^{26}D[c = 1, MeOH] = +79.0°$.

Mass spectrum, m/e (relative intensity) 273 (M^+ + 1,3) 229 (2), 214 (2), 184 (1), 165 (7), 157 (4), 140 (33), 139 (100), 138 (95), 97 (98), 96 (100), 91 (98).

Elemental analysis: calculated: 66.16% C; 5.92% H; 10.29% N. Found: 65.89% C; 5.86% H; 10.42% N.

COMPARATIVE EXAMPLE 8

Synthesis of N-Benzyl 2-Acetamidohydracrylamide

To an anhydrous THF solution (400 mL) of methyl-α-acetamido-N-benzylmalonamate (14.4 g, 54.5 mmol) was successively added dry LiCl (4.62 g, 109 mmol), $NaBH_4$ (4.13 g, 109 mmol) and EtOH (200 mL). The reaction mixture was stirred at room temperature (5h). The suspension was concentration <u>in vacuo</u>. After continuous extraction (12h) of the product using $CHCl_3$ (1000 mL) and H_2O (250 mL), the organic layer was collected, dried (Na_2SO_4), and removed <u>in vacuo</u> to give a crude white solid. The crude product was triturated with Et_2O (500 mL) to give 11.45 g (89%) of the above compound: mp 201-203°C; R_f0.40 (10% MeOH-$CHCl_3$); IR (KBr) 3287, 3085, 2969, 2859, 1648, 1552, 1456, 1055, 697 cm^{-1}; ^1H NMR (DMSO-d_6) δ1.88 (s, $C(O)CH_3$), 3.59 (dd, J = 5.7 Hz, 5.7 Hz, CH_2O), 4.19-4.35 (m, CH_2NH, CH), 4.92 (t, J = 5.7 Hz, OH), 7.10-7.40 (m, 5 PhH), 7.94 (d, J = 5.7 Hz, NH), 8.38 (t, J = 5.7 Hz, NH); ^{13}C NMR (DMSO-d_6) 22.2 ($C(O)CH_3$), 41.6 (CH_2N), 54.9 (CH), 61.3 (CH_2OH), 126.2 ($C_{4'}$), 126.5 ($2C_{2'}$ or $2C_{3'}$), 127.7 ($2C_{2'}$ or $2C_{3'}$), 138.9 ($C_{1'}$), 169.1 ($C(O)CH_3$ or C(O)NH), 169.9 ($C(O)CH_3$ or C(O)NH) ppm; MS (+Cl) (relative intensity) 237 (M^+ + 1, 100), 219 (9); M_r(+Cl) 237.123 88 [M^+ + 1] (calcd for $C_{12}H_{17}N_2O_3$ 237.123 92); Anal. ($C_{12}H_{16}N_2O_3$) C, H, N.

COMPARATIVE EXAMPLE 9

Synthesis of N-Benzyl 2-Acetamido-3-methoxypropionamide(racemic mixture)

To an CH_3CN solution (500 mL) of the product of Comparative Example 8 (2.36 g, 10 mmol) was successively added Ag_2O (11.59 g, 50.0 mmol) and CH_3I (6.23 mL, 100 mmol) at room temperature and then the reaction mixture was stirred at room temperature (4 d). The insoluble salts were filtered, and the solvent was removed in vacuo to give a white solid. The residue was triturated with Et_2O (50 mL) to give 2.10 g (84%) of the above-identified compound: mp 121-122°C; R_f 0.47 (10% MeOH-$CHCl_3$); IR (KBr) 3290, 3087, 2924, 2878, 2820, 1637, 1548, 1139, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.04 (s, $C(O)CH_3$), 3.38 (s, OCH_3), 3.43 (dd, J = 7.8, 9.0 Hz, $CHH'OCH_3$), 3.82 (dd, J = 4.2, 9.0 Hz, $CHH'OCH_3$), 4.48 (d, J = 6.0 Hz, $NHCH_2$), 4.51-4.57 (m, CH), 6.43 (br d, J = 5.4 Hz, NH), 6.74 (br s, NH), 7.25-7.37 (m, 5 PhH); ^{13}C NMR ($CDCl_3$) 23.2 ($C(O)CH_3$), 43.5 (CH_2N), 52.4 (CH), 59.1 (OCH_3), 71.7 (CH_2OCH_3), 127.4 ($C_{4'}$ and $2C_{2'}$ or $2C_{3'}$), 128.7 ($2C_{2'}$ or $2C_{3'}$), 137.8 ($C_{1'}$), 170.0 ($C(O)CH_3$ or $C(O)NH$), 170.3 ($C(O)CH_3$ or $C(O)NH$) ppm; MS (+CI) (relative intensity) 251 (M^+ + 1, 100), 219 (100); M_r(+CI) 251.139 39 [M^+ + 1] (calcd for $C_{13}H_{19}N_2O_3$ 251.139 57); Anal. ($C_{13}H_{18}N_2O_3$) C, H, N.

COMPARATIVE EXAMPLE 10

(S)-N-Benzyl 2-Acetamidohydracrylamide

To a stirred AcOH (20 mL) suspension of L-serine (2.63 g, 25 mmol) was added Ac_2O (2.5 mL, 26.3 mmol) and then the reaction suspension was stirred at room temperature (24h). The AcOH was removed in vacuo to given an oily residue, and then THF (150 mL) was added to the residue. The THF suspension was cooled to -78°C under N_2 and 4-methylmorpholine (5.5 mL, 50 mmol) was added. After stirring (2 min.), isobutyl chloroformate (6.5 mL, 50 mmol) was added leading to the precipitation of white solid. The reaction was allowed to proceed for two additional minutes and then benzylamine (5.5 mL, 50 mmol) was added at -78°C. The reaction mixture was allowed to stir at room temperature (30 min.) and then the 4-methylmorpholine hydrochloride salt was filtered. The organic layer was concentrated in vacuo. The product was purified by flash column chromatography on SiO_2 gel (10% MeOH-$CHCl_3$) to given 2.20 g (37%) of the above product as a white solid: mp 146-147°C; $[\alpha]_D^{23}$ (c = 1, MeOH) = -21.5°; ^{1}H NMR (DMSO-d_6) δ1.86 (s, C(O)CH_3), 3.57 (dd, J = 5.1 Hz, 5.1 Hz, CH_2O), 4.25-4.32 (m, CH_2NH, CH), 4.91 (t, J = 5.1 Hz, OH), 7.20-7.33 (m, 5 PhH), 7.93 (d, J = 8.1 Hz, NH), 8.37 (t, J = 5.7 Hz, NH), addition of excess (R)-(-)mandelic acid to a $CDCl_3$

solution of the above-identified compound gave only one signal for the acetyl methyl protons.

COMPARATIVE EXAMPLE 11

(S)-N-Benzyl 2-Acetamido-3-methoxypropionamide

To a stirred CH_3CN solution (300 mL) of the compound produced in Comparative Example 10 (1.18 g, 5 mmol) was successively added Ag_2O (5.80 g, 25 mmol) and MeI (3.1 mL, 10 mmol) at room temperature. The reaction mixture was stirred at room temperature (4d). The insoluble salts were filtered, and the solvent was removed _in vacuo_ to give a white solid. The white solid was triturated with Et_2O (100 mL) to give 1.00 g (80%) of the above-identified compound: mp 143-144°C $[\alpha]^{23}D$ (c = 1, MeOH) = -16.4°; ^1H NMR ($CDCl_3$) δ2.03 (s, $C(O)CH_3$), 3.38 (s, OCH_3), 3.43 (dd, J = 7.5, 9.0 Hz, $CHH'OCH_3$), 3.81 (dd, J = 4.2, 9.0 Hz, $CHH'OCH_3$), 4.47 (d, J = 5.7 Hz, $NHCH_2$), 4.52-4.59 (m, CH), 6.48 (br d, J = 6.0 Hz, NH), 6.81 (br s, NH), 7.25-7.37 (m, 5 PhH), addition of excess (R)-(-)-mandelic acid to a $CDCl_3$ solution of the above-identified compound gave only one signal for the acetyl methyl and ether methyl protons.

COMPARATIVE EXAMPLE 12

(R)-N-Benzyl 2-Acetamidohydracylamide

This compound was prepared in accordance with the procedures described in Examples 1 and 2.

PHARMACOLOGY

Compounds were screened under the auspices of the National Institutes of Health for anticonvulsant activity in both male albino Carthworth Farms No. 1 mice (ip route) and male albino Sprague Dawley rats (oral (po) route). Activity was established using the electrical (maximal electroshock or MES) test. In the MES test, a drop of electrolyte solution with anesthetic (0.5% butacaine hemisulfate in 0.9% sodium chloride) was used in the eyes of the animals prior to positioning the corneal electrodes and delivery of current. A 60 cycle alternating current was administered for 0.2 sec. in both species, 50 mA in mice and 150 mA in rats. Protection endpoints were defined as the abolition of the hind limb tonic extensor component of the induced seizure. In mice, effects of compounds on forced spontaneous motor activity were determined using the rotorod test. The inability of animals to maintain their balance for 1 min. on a 1 inch diameter knurled rod at 6 rpms in 3 successive trials demonstrated motor impairment. Normally under these conditions, a mouse can maintain its balance almost indefinitely. In rats, motor impairment is assessed by observing for overt evidence of ataxia, abnormal gait and stance, and/or loss of placing response and muscle tone. In the mouse identification screening study all compounds were

given at three dose levels (30, 100, 300 mg/kg) and two time periods (0.5, 4h). Typically, in the MES seizures test one animal was used at 30 mg/kg and 300 mg/kg, and three animals at 100 mg/kg. In the rotorod toxicity test four animals were used at 30 mg/kg, and 300 mg/kg, and eight animals at 100 mg/kg. If activity was found at 30 mg/Kg, then lower dosages were used to find the ED_{50} values.

The quantitative determination of the median effective (ED_{50}) and toxic doses (TD_{50}) were conducted at previously calculated times of peak effect. Groups of at least eight animals were tested using different doses of test compound until at least two points were determined between 100 and 0% protection and minimal motor impairment. The dose of candidate substance required to produce the defined endpoint in 50% of the animals in each test and the 95% confidence interval were calculated.

The results of various compounds of the present invention and comparative examples are provided in the accompanying table.

TABLE 1

Physical and Pharmacological Data for Functionalized N-Benzyl 2-Acetamidopropionamide Stereoisomers of the formula $ArCH_2NHC(O)CH(R^1)NHC(O)CH_3$

					mice(ip)[b]			rat(po)[f]		
No.	Stereochem.	R^1	Ar	m p[a]	MES,[c] ED_{50}	tox,[d] TD_{50}	PI[e]	MES,[c] ED_{50}	tox,[d] TD_{50}	PI[e]
Comp. Ex. 1	(R,S)	CH_3	Ph	138-139	76.5 [1] (66.6-89.0)	454 [0.5] (417-501)	5.9	48.2 [1] (32.0-71.8)	[h]	>20.8
Comp. Ex. 2	(R)	CH_3	Ph	139-141	54.8 [0.5] (50.3-59.7)	214 [0.5] (148-262)	3.9	28.4 [4] (22.4-35.0)	[h]	>35.2
Comp. Ex. 3	(S)	CH_3	Ph	139-142	548 [0.5] (50.3-59.7)	841 [0.5] (691-954)	1.5	[j]	[j]	[j]
Comp. Ex. 9	(R,S)	CH_2OCH_3	Ph	121-122	8.3 [0.5] (7.9-9.8)	42.9 [0.25] (38.1-46.8)	5.2	3.8 [2] (2.9-5.5)	386.8 [1] (316.0-514.6)	101.8
Ex. 1,2	(R)	CH_2OCH_3	Ph	143-144	4.5 [0.5] (3.7-5.5)	26.8 [0.25] (25.5-28.0)	6.0	3.9 [0.5] (2.6-6.2)	>500 [0.5]	>128.2
Comp. Ex.11	(S)	CH_2OCH_3	Ph	143-144	>100,<300	>300		>30	>30	[j]
Comp. Ex.8	(R,S)	CH_2OH	Ph	201-203	>100,<300	>300		[j]	[j]	[j]
Comp. Ex.12	(R)	CH_2OH	Ph	148-149	53.4 [2] (37.5-67.3)	>500 [2]	>9.4	[j]	[j]	[j]
Ex. 3	(R)	CH_2OCH_3	Ph(m-F)	150-151	6.9 [0.25] (6.1-8.0)	46.3 [0.25] (40.4-54.5)	6.7	6.9 [0.5] (4.3-9.9)	>396 [0.5]	>57.7
Ex. 4	(R)	CH_2OCH_3	Ph (p-F)	144-145	4.2 [0.5] (3.5-5.1)	27.8 [0.25] (22.4-33.5)	6.6	2.6 [2] (1.9-3.6)	>125,<250	[j]
Comp. Ex.4	(R,S)	OCH_3	Ph	145-146	98.30	7100<300	>1,<3	[j]	[j]	[j]
Comp. Ex.6	(R)	furyl	Ph	190-197	3.3	23.8	>.2	[j]	[j]	[j]
Comp. Ex.7	(S)	furyl	Ph	196-197	>25.	>200	[j]	[j]	[j]	[j]
Comp. Ex.5	(R,S)	furyl	Ph	178-179	10.3	-40	>3.9	[j]	[j]	[j]

[a] Melting points (°C) are uncorrected.
[b] The compounds were administered interperitoneally. ED_{50} and TD_{50} values are in mg/kg. Numbers in parentheses are 95% confidence intervals. The dose effect data was obtained at the "time of peak effect" (indicated in hours in the brackets).
[c] MES = maximal electroshock seizure test.
[d] Tox = neurologic toxicity determined from rotorod test.
[e] PI = protective index (TD_{50}/MES ED_{50}).
[f] The compounds were administered orally.
[h] No ataxia observed up to 1000 mg/kg.
[j] Data not available

As clearly shown by the above data, the R enantiomers of the present invention have quite potent anticonvulsant activity. The inventor has found that the R stereoisomer is unexpectedly more potent than the corresponding S stereoisomer and the racemic mixture. This conclusion is quite apparent from the data in the table which shows the R isomer in the mouse model is greater than 25 times more effective than both the corresponding S isomer and the racemic mixture, while in the rat model the R isomer is greater than 7 times more effective than the corresponding S isomer.

The data in the table clearly demonstrates that the efficacy of most compounds of the prior art i.e., the comparative examples depicted in the table, are significantly less than those of the present invention. Only the 2-furyl derivative in the Table shows comparable potency.

In addition, the compounds of the present invention have relatively low neurological toxicity, considering the efficacy thereof. In fact, as clearly shown by the data, the neurological toxicity is significantly lower in rats in which the compounds were administered orally than in the mice in which the compounds were administered intraperitoneally. In fact, in rats, the neurological toxicity of the compounds of the present invention is very low.

The PI values of the compounds of the present invention in the mice model in which the compound was administered intraperitoneally and especially in the rat model in which the compounds were administered orally, are quite high.

It is important to place the data in the table in proper perspective. Looking at the data, it is quite apparent that the compounds of the present invention exhibit an excellent drug profile. On the other hand, based upon the data, except for the furyl derivatives, the other comparative compounds are significantly inferior drugs relative to the compounds of the present invention. Although in some cases, the neurological toxicity of the compounds of the comparative examples is low and the PI value is satisfactory, the data cannot be viewed in a vacuum. It is preferred that the drug not have a low potency, even if it has a low neurological toxicity. After all, the objective is to administer as little drug as possible to obtain an efficacious result; the more drug administered to achieve a particular efficacious result, the greater will be the risk that the drug would have other effects, some of which are adverse, in other areas of the animal, including man, in need of such treatment. Thus, except for the furyl derivatives, based upon the data in the table the other comparative examples have a significantly poorer drug profile relative to the compounds of the present invention.

But, there is still another factor which must be taken into consideration. It is known that a major side effect of many anticonvulsants is liver toxicity. Thus, the liver toxicity of the furyl derivative was determined.

In the liver toxicity studies, various dosages such as 25 mg/kg, 100 mg/kg, 500 mg/kg of a particular drug was administered by oral gavage to rats for a set period of time. The rats were housed separately. The rats were periodically viewed for mortality and moribundity. At the termination of the study, the surviving rats were anesthesized, and exsanguinated under anesthesia. Complete necropsies were performed by appropriately trained personnel using procedures approved by board certified pathologists and the results were recorded.

When the D-furyl derivative of Comparative Example 5 was administered to the rat, hepatocellular necrosis was evident at 100 and 25 mg/kg in rats treated for 13 weeks.

On the other hand, the compounds of the present invention have significantly lower liver toxicity. These compounds of the present invention exhibit none or minimal effects at these lower dose levels.

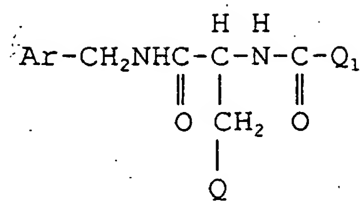
Thus, the compounds of the present invention exhibit an excellent drug profile. They meet all of the four characteristics outlined heretofore, high potency, low neurological toxicity relative to its

potency, high protective index and low liver toxicity. These compounds of the present invention exhibit advantages that have not heretofore been realized.

The above preferred embodiments and examples are given to illustrate the scope and spirit of the present invention. The embodiments and examples described herein will make apparent to those skilled in the art other embodiments and examples. These other embodiments and examples are within the contemplation of the present invention. Therefore, the present invention should be limited only by the appended claims.

WHAT IS CLAIMED IS:

1. A compound in the R configuration having the formula:



R

wherein

Ar is phenyl which is unsubstituted or substituted with at least one halo group;

Q is lower alkoxy, and

Q_1 is methyl.

2. The compound according to Claim 1 which is substantially enantiopure.

3. The compound according to Claim 1 wherein Q is lower alkoxy containing 1-3 carbon atoms.

4. The compound according to Claim 3 wherein Q is methoxy.

5. The compound according to Claim 1 wherein Ar is unsubstituted phenyl.

6. The compound according to Claim 1 wherein halo is fluoro.

7. The compound according to Claim 1 wherein Q is alkoxy containing 1-3 carbon atoms and Ar is unsubstituted phenyl.

8. The compound according to Claim 1 which is (R)-N-Benzyl 2-Acetamido-3-methoxypropionamide.

9. The compound according to Claim 8 which is substantially enantiopure.

10. A therapeutic composition comprising an anticonvulsant effective amount of a compound according to any one of Claims 1-9 and a pharmaceutical carrier therefor.

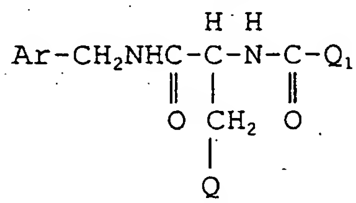
11. A method of treating central nervous system disorders in an animal comprising administering to said animal in need thereof an anticonvulsant effective amount of a compound according to any one of Claims 1-9.

12. The method according to Claim 11 wherein the animal is a mammal.

13. The method according to Claim 12 wherein the mammal is a human.

ABSTRACT

The present invention is directed to a compound in the R configuration about the asymmetric carbon in the following formula:



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pharmaceutical compositions containing same and the use thereof in treating CNS disorders in animals.